PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 317/44, 317/46, A61K 31/16

A1

(11) International Publication Number: **WO 98/34915**

(43) International Publication Date: 13 August 1998 (13.08.98)

(21) International Application Number: PCT/IB98/00101

(22) International Filing Date: 27 January 1998 (27.01.98)

(30) Priority Data:
60/037,402 7 February 1997 (07.02.97) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ROBINSON, Ralph, Pelton [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

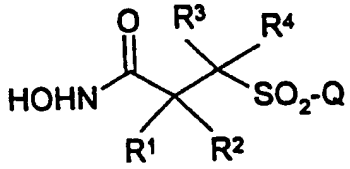
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: N-HYDROXY-BETA-SULFONYL-PROPIONAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF MATRIX METALLOPROTEINASES

(57) Abstract

A compound of formula (I) wherein R^1, R^2, R^3, R^4 and Q are as defined in the specification, to pharmaceutical compositions containing them and to their medicinal use as matrix metalloproteinases inhibitors and for the production of tumor necrosis factor (TNF).



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

N-HYDROXY-BETA-SULFONYL-PROPIONAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF MATRIX METALLOPROTEINASES

Background of the Invention

The present invention relates to arylsulfonylamino hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, such as AIDS, sepsis, or septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

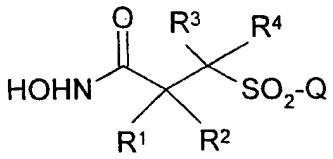
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g., osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g., corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g., Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

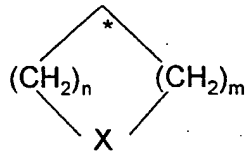
The present invention relates to a compound of the formula



wherein R^1 is hydrogen, hydroxy, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl(C=O)O-, (C_1-C_6)alkoxy(C=O)O-, (C_6-C_{10})aryl(C=O)O-, (C_6-C_{10})aryloxy(C=O)O-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-; wherein said aryl moiety of said (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_6-C_{10})aryl(C=O)O-, (C_6-C_{10})aryloxy(C=O)O-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O- groups is optionally substituted by one or more substituents (preferably one to three substituents) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

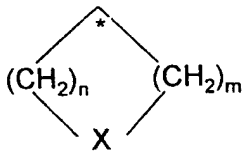
R^2 is hydrogen or (C_1-C_6)alkyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl(difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C=O)O-(C_1-C_6)alkyl , (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, $[(C_1-C_6)\text{alkyl}]_2$amino$(C_1-C_6)$alkyl, (C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, $R^5CO(C_1-C_6)$alkyl or $R^8(C_1-C_6)$alkyl; or R^3 and R^4 may be taken together with the carbon atom to which they are attached to form a (C_3-C_6)cycloalkyl or benzo-fused(C_3-C_6)cycloalkyl ring or a group of the formula



wherein the carbon atom bearing the asterisk is the carbon to which R^3 and R^4 are atttached, "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)alkyl(C=O)-, (C_1-C_6)alkoxy(C=O)-, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryloxy(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-; wherein each of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl or (C_3-C_6)cycloalkyl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-, (C_3-C_6)cycloalkyl, or benzo-fused(C_3-C_6)cycloalkyl ring may be optionally substituted on any ring atom capable of forming an additional bond by a substituent (preferably one to three substituents per ring) independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or when R^3 and R^4 are taken together with the carbon atom to which they are attached to form a group of the formula



then any of the carbon atoms of said ring, capable of forming an additional bond, may be optionally substituted by a substituent (preferably zero to three substituents) independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^5 is R^6O or R^6R^7N wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl; wherein each of said (C_6-C_{10})aryl and (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl groups may be optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or R^6 and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocycle selected from piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^8 is piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl,

piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, and (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

Q is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl wherein each (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents (preferably one to three substituents) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

with the proviso that if either R^3 or R^4 is hydrogen, or if both R^3 and R^4 are hydrogen, then R^1 and R^2 can not both be hydrogen or R^1 must be hydroxy, (C_1-C_6)alkoxy, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl,

$(C_6$-$C_{10})$aryl(C=O)O-$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryloxy(C=O)O- $(C_6$-$C_{10})$arylalkyl(C=O)O-$(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$arylalkoxy(C=O)O-$(C_1$-$C_6)$alkyl;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), trimethyl-ammonium or diethylammonium, and the lower alkanolammonium salts such tris-(hydroxymethyl)-methylammonium and other base salts of pharmaceutically acceptable organic amines.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl.

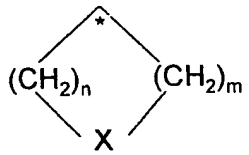
The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkoxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The compound of formula I may have chiral centers and therefore exist in different diasteriomeric or enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein R^1 is OH and R^2 is hydrogen.

Other preferred compounds of formula I include those wherein both R^3 and R^4 are $(C_1\text{-}C_6)$alkyl or R^3 and R^4 are taken together to form an optionally substituted $(C_3\text{-}C_6)$cycloalkyl ring or a benzo-fused$(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula



wherein the carbon atom bearing the asterisk is the carbon to which R^3 and R^4 are atttached, "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-; wherein each of said $(C_6\text{-}C_{10})$aryl and $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, and $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents (preferably one to three substituents) independently selected from the group consisting of fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy.

More preferred compounds of formula I include those wherein R^3 and R^4 are taken together to form an optionally substituted $(C_3\text{-}C_6)$cycloalkyl ring.

Other preferred compounds of formula I include those wherein R^1 is hydroxy.

Other preferred compounds of formula I include those wherein Q is $(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, wherein each $(C_6\text{-}C_{10})$aryl moieties of said is $(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl groups may be optionally substituted with one or more substituents

independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

More preferred compounds of formula I include those wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl, more preferably the substituents are selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, most preferably the substituent is in the 4-position.

Specific preferred compounds of formula I include the following:

(2S)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide,

3-[4-(4-fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide,

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide.

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclopentyl]acetamide,

2-[1-(4-cyclobutoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}-2,N-dihydroxyacetamide, or

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}-2,N-dihydroxyacetamide.

Other specific compounds of formula I include the following:

2,N-dihydroxy-2-[1-(4-phenoxybenzenesulfonyl)cyclopentyl]acetamide,

2,N-dihydroxy-2-[1-(4-phenoxybenzenesulfonyl)cyclobutyl]acetamide,

acetic acid {1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}hydroxycarbamoyl methyl ester,

acetic acid {1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}hydroxycarbamoyl methyl ester,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}-N-hydroxy-2-methoxy-acetamide,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}-N-hydroxy-2-methoxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclohexyl]-2,N-dihydroxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclopentyl]-2,N-dihydroxyacetamide, or

2-[1-(4-butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, osteoporosis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic

shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

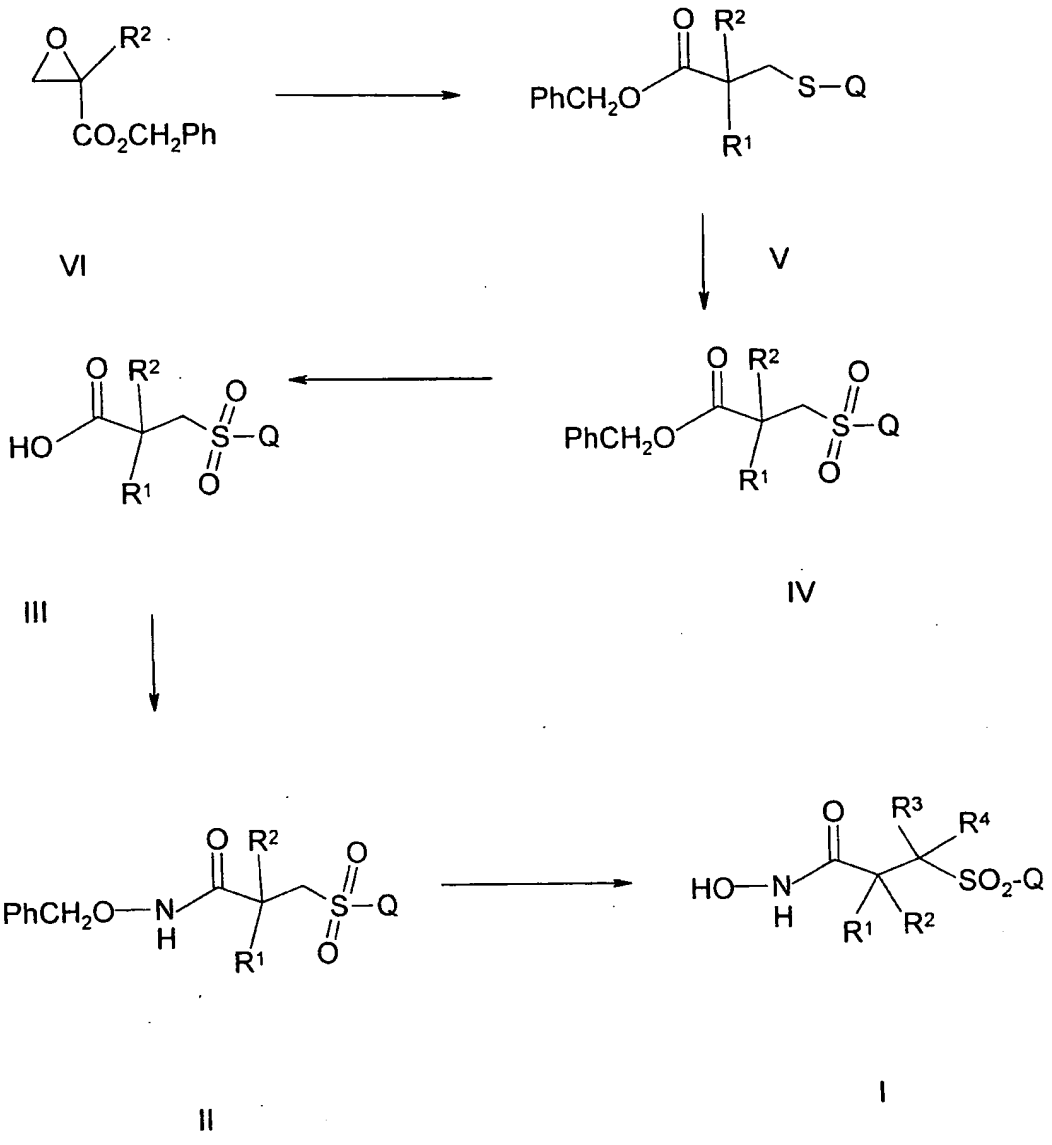
The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

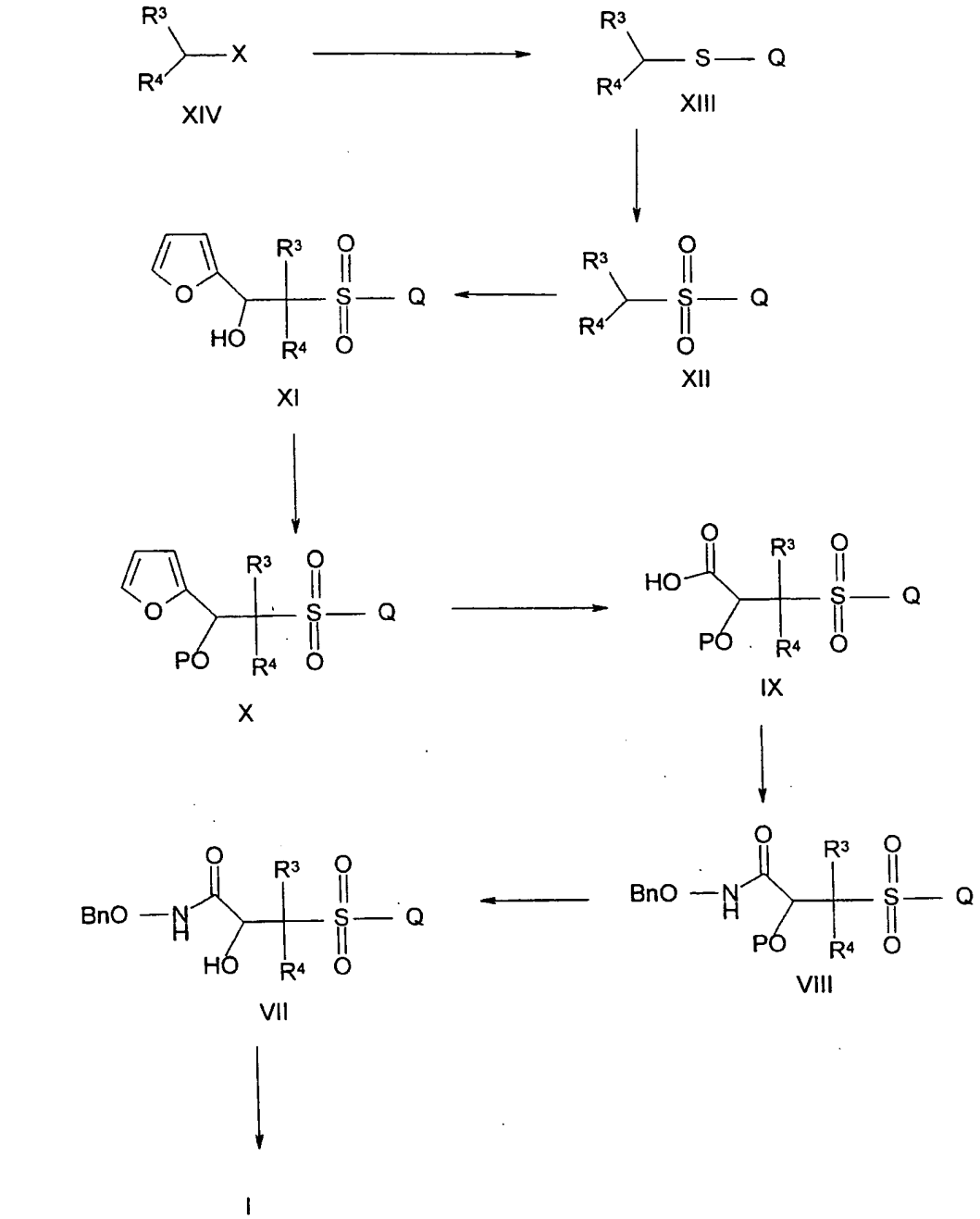
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated n, m, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, Q and X in the reaction Schemes and the discussion that follow are defined as above.

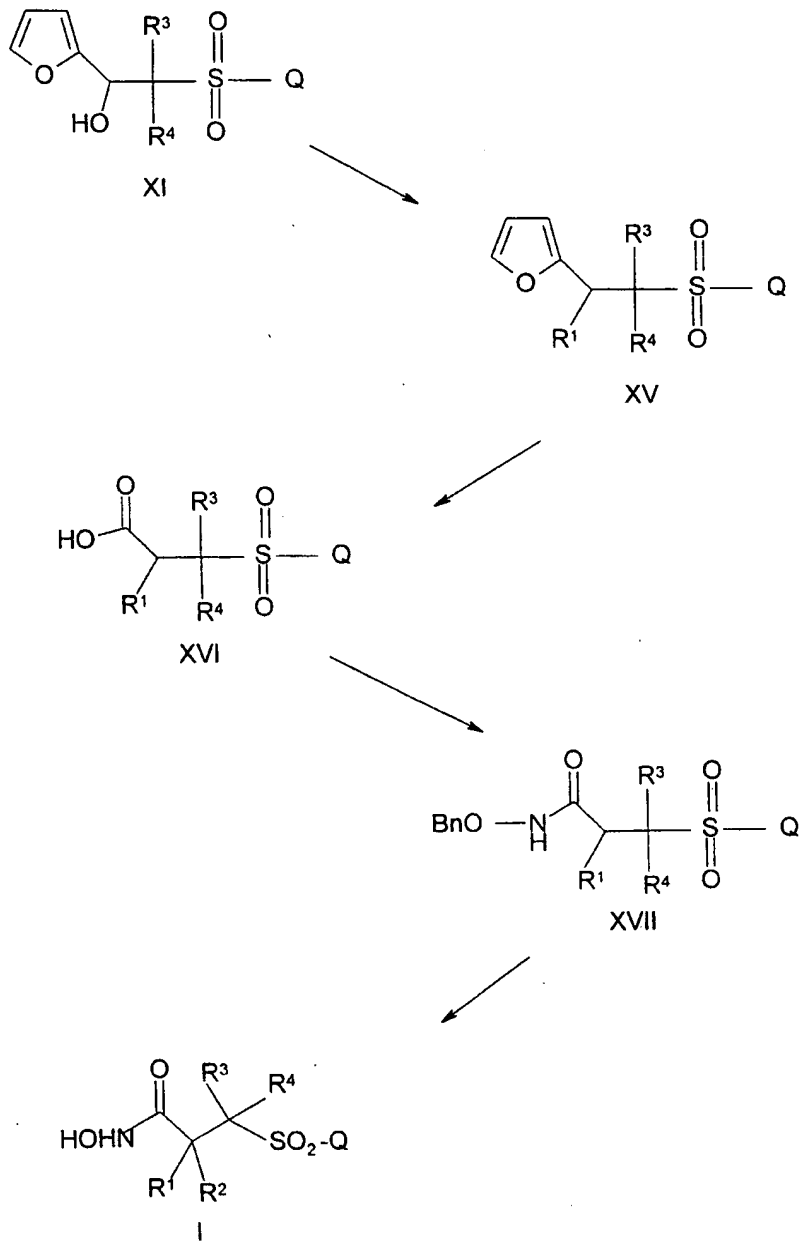
SCHEME 1



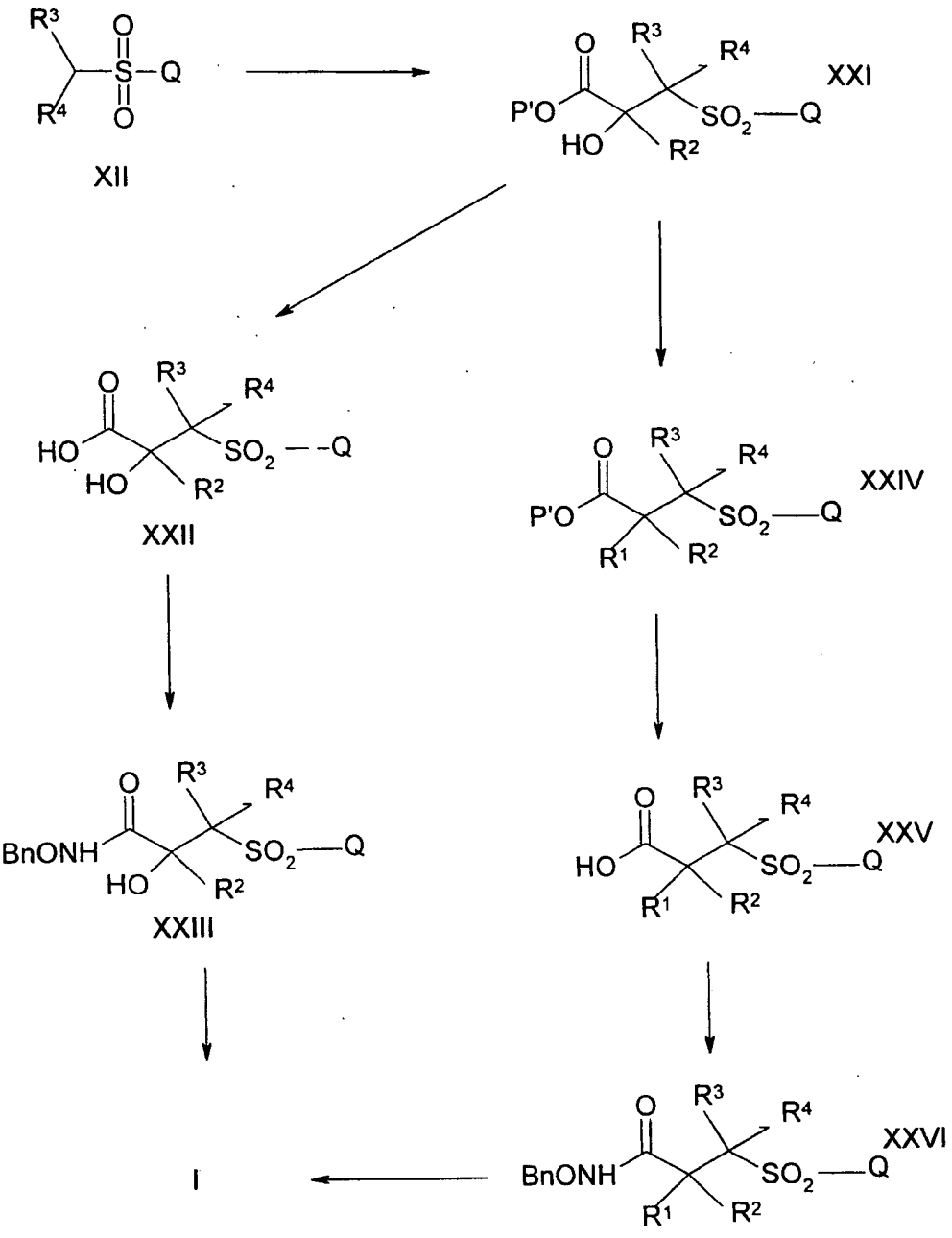
SCHEME 2



SCHEME 3



SCHEME 4



Scheme 1 refers to the preparation of compounds of the formula I, wherein R^3 and R^4 are hydrogen. Referring to Scheme I, a compound of the formula I is prepared from a compound of the formula II by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

The compound of formula II is prepared from a compound of formula III by reaction with O-benzylhydroxylamine hydrochloride, an activating agent, and a base in a reaction inert solvent. Suitable activating agents include (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably triethylamine. The temperature of the aforesaid reaction may range from about 0°C to about 60°C, preferably about 20°C (room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, or ethers such as THF or diethyl ether, preferably the solvent is methylene chloride. The reaction is complete in about 4 hours to about 48 hours, preferably about 16 hours.

The compound of formula III is prepared from a compound of formula IV by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include palladium or 5-10% palladium on activated charcoal, preferably 10% palladium on activated charcoal. Suitable solvents include acetic acid, alcohols such as ethanol, methanol, or isopropanol, preferably ethanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula IV can be prepared from compounds of the formula V by reaction with an oxidant in a reaction inert solvent. Suitable oxidants include meta-

chloroperbenzoic acid, hydrogen peroxide or sodium perborate, preferably meta-chloroperbenzoic acid. Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. Suitable temperatures for the aforesaid reaction range from about 0°C to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula V, wherein R^1 is hydroxy, can be prepared from compounds of the formula VI by reaction with a Grignard reagent and a thiol of the formula QSH in a reaction inert solvent. Suitable Grignard reagents include ethyl magnesium bromide or phenyl magnesium bromide, preferably ethyl magnesium bromide. Suitable solvents include ethers such as diethyl ether, tetrahydrofuran or 1,2-dimethoxyethane, preferably the solvent is a mixture of tetrahydrofuran and diethyl ether. Suitable temperatures for the aforesaid reaction are from about -78°C to about 50°C , preferably from about 0°C to about 25°C (i.e. room temperature). The reaction is complete in about 1 to about 24 hours, preferably about 3 hours.

Compounds of the formula V, wherein R^1 is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy or $(C_1\text{-}C_6)$alkoxy, can be prepared from compounds of the formula V, wherein R^1 is hydroxy, by reaction with a compound of the formula $R^{1a}L$, wherein L is a leaving group and R^{1a} is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkyl, in the presence of a strong base in an aprotic polar solvent. Suitable leaving groups include chloro, fluoro, bromo, mesylate, triflate or tosylate. Preferably, the leaving group is iodo. Suitable bases include sodium hydride, lithium dialkyl amides such as lithium N-isopropyl-N-cyclohexylamide or lithium diisopropyl amide, potassium t-butoxide, sodium amide, or potassium hydride, preferably sodium hydride. Suitable solvents include ethers (such as THF, diethyl ether or 1,2-dimethoxyethane), preferably THF. The aforesaid reaction is conducted at about -78°C to about 0°C, preferably at about 0°C.

Compounds of the formula V, wherein R^1 is $(C_1\text{-}C_6)$alkyl(C=O)O-, $(C_1\text{-}C_6)$alkoxy-(C=O)O-, $(C_6\text{-}C_{10})$aryl(C=O)O-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)O- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)O-, can be prepared from compounds of the formula V, wherein R^1 is hydroxy, by reaction with a compound of the formula $R^{1b}L$, wherein L is a leaving group and R^{1b} is $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryloxy(C=0)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-, in the presence of a base in a reaction inert solvent. Suitable leaving groups include chloro, fluoro, bromo, or $R^{1b}O$ (i.e. an anhydride). Preferably, the leaving group is chloro. Suitable bases include tertiary amine bases such as triethylamine, pyridine or 4-dimethylaminopyridine, preferably triethylamine. The temperature of the aforesaid reaction is from about 0°C to about 30°C, preferably from

about 20°C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 1 hour to about 24 hours, preferably for about 2 hours.

Compounds of the formula VI can be prepared by methods well known to those of ordinary skill in the art. Compounds of the formula VI can also be prepared by peracid oxidation (e.g., meta-chloroperbenzoic acid) of the corresponding α,β-unsaturated benzyl esters as described in Jerry March, Advanced Organic Chemistry, 735 (3rd ed., 1985). The corresponding α,β-unsaturated benzyl esters may be prepared by Knovenagel condensation between a malonate monobenzyl ester and paraformaldehyde in the presence of piperidine as described in H.O. House, Modern Synthetic Reactions, 649-651 (2nd ed., W.A. Benjamin, Menlo Park, California, 1972).

Compounds of the formula VI, wherein R^2 is hydrogen, can also be prepared in racemic or enantiomerically pure form by conversion of L-, D-, or D,L-serine as reported by W. Roush and B. Brown, J. Org. Chem., 47, 3387 (1992).

Scheme 2 refers to the preparation of compounds of the formula I, wherein R^2 is hydrogen and R^1 is OH. Referring to Scheme 2, compounds of formula I can be prepared from compounds of the formula VII by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

Compounds of the formula VII can be prepared from compounds of the formula VIII by reaction with an alkali metal hydroxide in a polar solvent. Suitable alkali metal hydroxides include lithium hydroxide, sodium hydroxide or potassium hydroxide, preferably lithium hydroxide, most preferably about 5 equivalents of the alkali metal hydroxide. The aforesaid reaction may conducted at a temperature from about 0°C to about 60°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include a mixture of water and an alcohol such as methanol or ethanol and, optionally an water miscible ether such as tetrahydrofuran or 1,2-dimethoxyethane. Preferably, the solvent system is methanol/water/tetrahydrofuran. The reaction is conducted from about 1 to about 72 hours, preferably about 24 hours.

The compound of formula VIII is prepared from a compound of the formula IX by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent. Suitable catalysts include (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine. diisopropylethylamine or dimethylaminopyridine, preferably triethylamine. The aforesaid reaction temperature is from about 0° C to about 60°C, preferably from about 20° C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 4 hours to about 48 hours, preferably about 16 hours.

The compound of formula IX is prepared from a compound of the formula X by reaction with an excess of sodium periodate in the presence of catalytic ruthenium trichloride hydrate. The aforesaid reaction is conducted at a temperature from about 0°C to about 35°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include acetone or a mixture of acetonitrile, carbon tetrachloride and water, preferably a 1:1:2 mixture of acetonitile, carbon tetrachloride and water. The reaction is conducted from about 0.5 to about 2 hours, preferably about 1.25 hours.

The compound of the formula X, wherein "P" is pivaloyl, acetyl or benzoyl, is prepared by reaction of a compound of the formula XI with a protecting group reagent in the presence of a base in a reaction inert solvent. Suitable protecting group reagents include pivaloyl chloride, pivaloic anhydride, acetyl chloride, acetic anhydride, benzoyl cloride or benzoic anhydride, preferably acetic anhydride. Suitable bases include tertiary amine bases such as pyridine or 4-N,N-dimethylaminopyridine, preferably 4-N, N-dimethylaminopyridine. The temperature of the aforesaid reaction is from about 0°C to about 30°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 1 hour to about 24 hours, preferably for about 2 hours.

The compound of formula XI is prepared from a compound of the formula XII by reaction with 2-furaldehyde and a strong base in a polar aprotic solvent. Suitable bases include potassium-tert.-butoxide, lithium diisopropylamide, and butyl lithium, preferably 2.5 M n-butyllithium in hexane. The temperature of the aforesaid reaction is from about -78°C to about 0°C, preferably about -78°C. Suitable solvents include diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane, preferably the solvent is tetrahydrofuran. The reaction is conducted from about 0.25 hours to about 6 hours, preferably about 0.33 hours.

The compound of formula XII is prepared from a compound of the formula XIII by reaction with an oxidant in a reaction inert solvent. Suitable oxidants include meta-chloroperbenzoic acid, hydrogen peroxide or sodium perborate, preferably meta-chloroperbenzoic acid. Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. Suitable temperatures for the aforesaid reaction range from about 0°C to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

The compound of the formula XIII is prepared from a compound of the formula XIV by reaction with a thiol of the formula QSH in the presence of a base in an aprotic solvent. Suitable bases include sodium hydride, ethyl magnesium bromide, lithium diisopropyl amide, potassium hydride, or sodium methoxide, preferably sodium hydride. The temperature of the aforesaid reaction is from about 0°C to about 60°C, preferably 20°C to about 25°C (i.e. room temperature). Suitable solvents include aprotic solvents such as methylene chloride, tetrahydrofuran or N,N-dimethylformamide, preferably N,N-dimethylformamide. The reaction is conducted for about 1 hour to about 48 hours, preferably about 16 hours.

Compounds of the formula XIV and QSH are commercially available or can be made by methods well known to those of ordinary skill in the art. Compounds of the formula QSH can also be prepared by reaction of an alkyl or aryl halide with sodium sulfhydride as described in Jerry March, Advanced Organic Chemistry, 360 and 589 (3rd ed., 1985). Alternatively, compounds of the formula QSH can also be prepared by reaction of an aryl diazonium salt with sodium sulfhydride as described in March id. at 601. Alternatively, compounds of the formula QSH can also be prepared by reaction of a Grignard reagent with sulfur as described in March id. at 550. Alternatively, compounds of the formula QSH can also be prepared by reduction of a sulfonyl chloride, sulfonic acid or disulfide as described in March id. at 1107 and 1110.

Scheme 3 refers to the preparation of compounds of the formula I, wherein R^1 is other than hydroxy and R^2 is hydrogen.

Referring to Scheme 3, compounds of the formula I are prepared from compounds of the formula XVII by hydrogenolysis according to methods analogous to the methods described for converting compounds of formula VII to compounds of formula I in Scheme 2.

Compounds of the formula XVII are prepared from compounds of the formula XVI by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent according to methods analogous to the conversion of compounds of the formula IX to formula VIII as described above in Scheme 2.

Compounds of the formula XVI are prepared from compounds of the formula XV by reaction with an excess of sodium periodate in the presence of a catalyst according to methods analogous to those used for the conversion of compounds of the formula X to formula IX as described above in Scheme 2.

Compounds of the formula XV, wherein R^1 is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy or $(C_1\text{-}C_6)$alkoxy, can be prepared from compounds of the formula XI by reaction with a compound of the formula $R^{1a}L$, wherein L is a leaving group and R^{1a} is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkyl, in the presence of a strong base in an aprotic polar solvent. Suitable leaving groups include chloro, fluoro, bromo, mesylate, triflate or tosylate. Preferably, the leaving group is iodo. Suitable bases include lithium dialkyl amides such as lithium N-isopropyl-N-cyclohexylamide or lithium diisopropyl amide, potassium t-butoxide, sodium amide, potassium hydride or sodium hydride, preferably sodium hydride. Suitable solvents include ethers (such as THF, diethyl ether or 1,2-dimethoxyethane), preferably THF. The aforesaid reaction is conducted at about -78°C to about 0°C, preferably at about 0°C.

Compounds of the formula XV, wherein R^1 is $(C_1\text{-}C_6)$alkyl(C=O)O-, $(C_1\text{-}C_6)$alkoxy(C=O)O-, $(C_6\text{-}C_{10})$aryl(C=O)O-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)O- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)O-, can be prepared from compounds of the formula XI by reaction with a compound of the formula $R^{1b}L$, wherein L is a leaving group and R^{1b} is $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-, in the presence of a base in a reaction inert solvent. Suitable leaving groups include chloro, fluoro, bromo or (R^{1b})O- (i.e. an anhydride). Preferably, the leaving group is chloro. Suitable bases include tertiary amine bases such as triethylamine, pyridine or 4-dimethylaminopyridine, preferably triethylamine. The temperature of the aforesaid reaction is from about 0°C to about 30°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 1 hour to about 24 hours, preferably for about 2 hours.

Compounds of the formula XI can be made according to the methods of Scheme 2.

Scheme 4 refers to the preparation of compounds of the formula I, wherein R^2 is other than hydrogen and R^3 and R^4 are other than hydrogen.

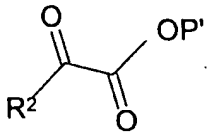
Referring to Scheme 4, compounds of the formula I are prepared from compounds of the formula XXIII by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents

include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

The compound of the formula XXIII is prepared from a compound of the formula XXII by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent. Suitable catalysts include (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine. diisopropylethylamine or dimethylaminopyridine, preferably triethylamine. The aforesaid reaction temperature is from about 0° C to about 60°C, preferably from about 20° C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 4 hours to about 48 hours, preferably about 16 hours.

The compound of the formula XXII can be prepared by deprotection of a compound of the formula XXI by reaction with an alkali metal hydroxide in a polar solvent. Suitable alkali metal hydroxides include lithium hydroxide, sodium hydroxide or potassium hydroxide, preferably lithium hydroxide, most preferably about 5 equivalents of the alkali metal hydroxide. The aforesaid reaction may conducted at a temperature from about 0°C to about 60°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include a mixture of water and an alcohol such as methanol or ethanol and, optionally an water miscible ether such as tetrahydrofuran or 1,2-dimethoxyethane. Preferably, the solvent system is methanol/water/tetrahydrofuran. The reaction is conducted from about 1 to about 72 hours, preferably about 24 hours.

Compounds of the formula XXI can be prepared from compounds of the formula XII by reaction with a compound of the formula



XXVII

wherein P' is methyl, ethyl or benzyl, and a strong base in a polar aprotic solvent. Suitable bases include sodium hydride (NaH), potassium-tert.-butoxide, lithium diisopropylamide, and butyl lithium, preferably 2.5 M n-butyllithium in hexane. The temperature of the aforesaid reaction is from about -78°C to about 0°C, preferably about -78°C. Suitable solvents include diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane, preferably the solvent is tetrahydrofuran. The reaction is conducted from about 0.25 hours to about 6 hours, preferably about 0.33 hours.

Alternatively, compounds of the formula I, wherein R^1 is other than hydroxy, R^2 is other than hydrogen and R^3 and R^4 are other than hydrogen, can be prepared from compounds of the formula XXV by methods analogous to the conversion of compounds of the formula XXII to compounds of formula I, as described above in Scheme 4.

Compounds of the formula XXV can be prepared from compounds of the formula XXIV, wherein P' is benzyl, by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include palladium or 5-10% palladium on activated charcoal, preferably 10% palladium on activated charcoal. Suitable solvents include acetic acid, alcohols such as ethanol, methanol, or isopropanol, preferably ethanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula XXIV, wherein R^1 is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy, can be prepared from compounds of the formula XXI by reaction with an arylalkyl or alkyl halide in the presence of a base in an aprotic solvent. Suitable bases include sodium hydride, ethyl magnesium bromide, lithium diisopropyl amide, potassium hydride, or sodium methoxide, preferably sodium hydride. The temperature of the aforesaid reaction is from about 0°C to about 60°C, preferably 20°C to about 25°C (i.e. room temperature). Suitable solvents include aprotic solvents such as methylene chloride, tetrahydrofuran or N,N-dimethylformamide, preferably N,N-dimethylformamide. The reaction is conducted for about 1 hour to about 48 hours, preferably about 16 hours.

Alternatively, compounds of the formula XXIV, wherein R^1 is $(C_1\text{-}C_6)$alkyl(C=O)O-, $(C_1\text{-}C_6)$alkoxy(C=O)O-, $(C_6\text{-}C_{10})$aryl(C=O)O-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)O- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)O-, can be prepared from compounds of the formula XXI by reaction with an arylacyl or acyl halide in the presence of a base in an aprotic solvent. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably triethylamine. The

temperature of the aforesaid reaction may range from about 0°C to about 60°C, preferably about 20°C (room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, or ethers such as THF or diethyl ether, preferably the solvent is methylene chloride. The reaction is complete in about 4 hours to about 48 hours, preferably about 16 hours.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic

compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 mg trypsin per 100 mg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ——> 120 μM ——> 12 μM ——> 1.2 μM ——> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 ml is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 mM in assay buffer. The assay is initiated by the addition of 50 ml substrate per well of the microfluor plate to give a final concentration of 10 mM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each

concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 mM then the inhibitors are assayed at concentrations of 0.3 mM, 0.03 mM, 0.03 mM and 0.003 mM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 mM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 mM, 3 mM, 0.3 mM and 0.03 mM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, then the inhibitors are assayed at final concentrations of 0.3 mM, 0.03 mM, 0.003 mM and 0.003 mM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-SCH[$CH_2CH(CH_3)_2$]CO-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 ml of a 10 mg/ml trypsin stock per 26 mg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 ml of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 ml of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 mg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 ml per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 mL to the appropriate wells yields final concentrations of 3 mM, 0.3 mM, 0.003 mM, and 0.0003 mM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 ml to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20mM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 mM, 3mM, 0.3 mM, and 0.03 mM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 ml is added to each well to give a final assay concentration of 10 mM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mM, 0.003 mM and 0.0003 mM.

All of the compounds of the invention that were tested in the Inhibition of MMP-13 assay had IC_{50}'s of less than 50nm.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180m of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200ml. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit®.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the active compound will be administered at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes. and, if so desired, emulsifying and/or suspending agents as well,

together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under

nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

Example 1

(2*S*)-2,N-DIHYDROXY-3-(4-METHOXYBENZENESULFONYL)PROPIONAMIDE

(A) (2*S*)-2-Hydroxy-3-(4-methoxyphenylsulfanyl)propionic acid benzyl ester

A solution of 1 M ethylmagnesium bromide in diethyl ether (16.6 mL, 16.7 mmole) was diluted with tetrahydrofuran (32 mL) and cooled in an ice bath. A solution of 4-methoxybenzenethiol (2.3 grams, 16.7 mmole) in anhydrous tetrahydrofuran (5 mL) was added dropwise. The resulting mixture was allowed to stir at 0°C for 1 hour and then a solution of benzyl (2*S*)-glycidate (2.3 grams, 12.9 mmole) in tetrahydrofuran (5 mL) was added. The mixture was stirred at room temperature for 3 hours. After quenching with water, the mixture was extracted with ether. The aqueous layer was acidified to pH 5 and again extracted with diethyl ether. The combined diethyl ether extracts were washed with water and brine, dried over magnesium sulfate and concentrated to an oil. The product, (2*S*)-2-hydroxy-3-(4-methoxyphenylsulfanyl)propionic acid benzyl ester (3.6 grams, 88%) was isolated as a light yellow oil by chromatography on silica gel using 1:1 diethyl ether/hexane as eluant.

(B) (2*S*)-2-Hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester

A solution of (2*S*)-2-hydroxy-3-(4-methoxyphenylsulfanyl)propionic acid benzyl ester (3.6 grams, 11 mmole) in methylene chloride (25 mL) was cooled in an ice bath and a solution of 50% m-chloroperbenzoic acid (8.4 grams, 24 mmole) in methylene chloride (75 mL) was added dropwise. The resulting mixture was stirred at room temperature for 4 hours. After quenching with saturated aqueous sodium bisulfite solution, the mixture was extracted with diethyl ether. The extract was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated to a white solid. Recrystallization from 1:1 hexane/ethyl acetate afforded (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester (3.2 grams, 84%) as a white crystalline solid.

(C) (2*S*)-2-Hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid

A solution of (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester (1.0 grams, 2.8 mmole) in methanol (70 mL) was treated with 10% palladium on activated carbon (100 mg) and hydrogenated at 3 atmospheres pressure for 3 hours in a Parr shaker. The catalyst was removed by filtration through diatomaceous earth and the filtrate was concentrated

to afford (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid as a white foam (729 mg, 100%).

(D) (2*S*)-N-Benzyloxy-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionamide

To a solution of (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid (800 mg, 3.0 mmole), O-benzylhydroxylamine hydrochloride (526 mg, 3.3 mmole) and triethylamine (1.2 mL, 9.0 mmole) in methylene chloride (80 mL) was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.4 grams, 3.3 mmole). The reaction mixture was stirred at room temperature for 16 hours and was then diluted with methylene chloride. The solution was washed successively with saturated aqueous sodium bicarbonate solution, water, 0.5 M aqueous hydrochloric acid solution and saturated brine. After drying over magnesium sulfate, the solvent was evaporated to afford an oil. The desired product, (2*S*)-N-benzyloxy-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionamide (400 mg, 36%), was isolated by flash chromatography on silica gel eluting successively with chloroform, 1% methanol in chloroform and 2% methanol in chloroform.

(E) (2*S*)-2,N-Dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide

A solution of (2*S*)-N-benzyloxy-2-hydroxy-3-(4-methoxybenzenesulfonyl) propionamide (400 mg, 1.0 mmole) in methanol (30 mL) was treated with 5% palladium on barium sulfate (200 mg) and hydrogenated at 3 atmospheres pressure for 4 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 μm nylon filter and the filtrate was concentrated. The desired product, (2*S*)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl) propionamide(180 mg, 65%), was isolated by flash chromatography on silica gel eluting with 5% methanol in chloroform followed by recrystallization from chloroform/methanol.

Melting point 138-144°C; MS m/z 276 (M+1); analysis calculated for $C_{10}H_{13}NO_6S$: C, 43.63; H, 4.76; N, 5.09. Found: C, 43.51; H, 4.68; N, 4.95.

Example 2

3-[4-(4-FLUOROPHENOXY)PHENYLSULFONYL]-2,N-DIHYDROXYPROPIONAMIDE

3-[4-(4-Fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide was prepared by a method analogous to that described in Example 1 using (4-fluorophenoxy)phenylthiol as starting material. Recrystallized from chloroform.

Melting point 129-130°C; MS m/z 356 (M+1); analysis calculated for $C_{15}H_{14}FNO_6S.0.75H_2O$: C, 48.84; H, 4.24; N, 3.80. Found: C, 49.03; H, 4.06; N, 3.86.

Example 3

2,N-DIHYDROXY-2-[1-(4-METHOXYBENZENESULFONYL)CYCLOBUTYL]ACETAMIDE

(A) 1-Cyclobutylsulfanyl-4-methoxybenzene

4-Methoxybenzenethiol (5.7 g, 40.7 mmole) was added to a suspension of sodium hydride (1.17 grams, 49 mmole) in dry N,N-dimethylformamide (50 mL). After stirring for 1 hour, cyclobutylbromide (6.0 grams, 44.4 mmole) was added. The reaction mixture was stirred for 16 hours and was quenched by addition of saturated aqueous ammonium chloride solution. The solvents were evaporated. The residue was taken up in diethyl ether and washed successively with 0.5 N aqueous hydrochloric acid solution, water and brine. After drying over magnesium sulfate, the diethyl ether was evaporated to afford 1-cyclobutylsulfanyl-4-methoxybenzene as an oil (7.9 grams, 100%).

(B) 1-Cyclobutylsulfonyl-4-methoxybenzene

A solution of 1-cyclobutylsulfanyl-4-methoxybenzene (7.9 grams, 40.7 mmole) in methylene chloride (50 mL) was cooled in an ice bath and a solution of 57% m-chloroperbenzoic acid (28 grams, 92 mmole) in methylene chloride (100 mL) was added dropwise. The resulting mixture was stirred at room temperature for 7 days. After quenching with saturated aqueous sodium bisulfite solution, the mixture was filtered to remove a white precipitate and extracted with methylene chloride. The extract was washed successively with saturated aqueous sodium bicarbonate solution, water and brine. After drying over magnesium sulfate, the solution was concentrated to a white solid. Recrystallization from ethyl acetate afforded 1-cyclobutylsulfonyl-4-methoxyhenzene (7.28 grams, 79%) as a white crystalline solid.

(C) Furan-2-yl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methanol

A solution of 1-cyclobutylsulfonyl-4-methoxybenzene (4.0 grams, 17.7 mmole) in dry tetrahydrofuran (80 mL) was cooled to -78°C and a 2.5 M solution of n-butyllithium in hexane was added. The mixture was allowed to warm to -50°C and was again cooled to -78°C. 2-Furaldehyde (4 mL, 48 mmole) was then added. After stirring for 20 minutes at -78°C, the reaction was quenched by addition of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate. The organic extract was washed with water and brine and was dried over magnesium sulfate. Evaporation of the solvent gave an oil from which furan-2-yl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]-methanol (4.3 grams, 75%) was isolated by flash chromatography on silica gel eluting with 1:3 ethyl acetate/hexane.

(D) 2,2-Dimethylpropionic acid furan-2-yl[1-(4-methoxybenzenesulfonyl)cyclobutyl]-methyl ester

A solution of furan-2-yl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methanol (1.57 grams, 4.9 mmole) and 4-dimethylaminopyridine (0.89 grams, 7.3 mmole) in methylene chloride (50 mL) was cooled in an ice bath. Pivaloyl chloride (0.66 mL, 5.4 mmole) was added. The mixture was stirred at 0°C for 2 hours, diluted with methylene chloride and extracted successively with 0.5 N aqueous hydrochloric acid and brine. After drying over $MgSO_4$, the solvent was evaporated to leave an oil from which the desired product, 2,2-

dimethylpropionic acid furan-2-yl[1-(4-methoxybenzenesulfonyl)cyclobutyl]methyl ester (1.60 grams, 81%), was isolated by flash chromatography eluting with 16% ethyl acetate in hexane.

(E) 2,2-Dimethylpropionic acid carboxy[1-(4-methoxybenzenesulfonyl)cyclobutyl] methyl ester

To a solution of 2,2-dimethylpropionic acid furan-2-yl[1-(4-methoxybenzenesulfonyl)-cyclobutyl]methyl ester (1.6 grams, 3.94 mmol) in acetonitrile (12 mL), carbon tetrachloride (12 mL) and water (22 mL) at room temperature were added, sequentially, sodium periodate (6.73 grams, 31 mmole) and ruthenium (III) chloride hydrate (21 mg). The mixture was stirred at room temperature for 1.25 hours and was then diluted with water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The combined organic fractions were dried over magnesium sulfate to yield the crude product, 2,2-dimethylpropionic acid carboxy[1-(4-methoxybenzenesulfonyl)cyclobutyl]-methyl ester, as an oil.

(F) 2,2-Dimethylpropionic acid benzyloxycarbamoyl-[1-(4-methoxybenzene sulfonyl)-cyclobutyl]methyl ester

The entire crude sample of 2,2-dimethylpropionic acid carboxy[1-(4-methoxybenzene-sulfonyl)cyclobutyl]methyl ester obtained in Step E was dissolved in methylene chloride (60 mL). O-Benzylhydroxylamine hydrochloride (0.69 grams, 4.3 mmol), triethylamine (1.6 mL, 11.5 mmole) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.91 grams, 4.3 mmole) were then added sequentially. The mixture was stirred at room temperature for 16 hours and was then concentrated under vacuum. The residue was taken up in ethyl acetate and the resulting solution was washed successively with 0.5 M aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution and brine. After drying over magnesium sulfate, the solvent was evaporated to afford an oil. The desired product, 2,2-dimethylpropionic acid benzyloxycarbamoyl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methyl ester (0.87 grams, 46%), was isolated by flash chromatography on silica gel eluting with 30% ethyl acetate in hexane.

(G) N-Benzyloxy-2-hydroxy-2[1-(4-methoxybenzenesulfonyl)cyclobutyl] acetamide

To a solution of 2,2-dimethylpropionic acid benzyloxycarbamoyl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methyl ester (0.87 grams, 1.78 mmol) in methanol (10 mL), tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide hydrate (0.37 grams, 8.8 mmol). The mixture was stirred at room temperature for 24 hours. Methanol-washed Amberlite IR-120 ion exchange resin (6 grams) was then added. After stirring for 15 minutes, the mixture was filtered. The filtrate was concentrated and the residue was taken up in ethyl acetate. The resulting solution was washed with saturated sodium bicarbonate

solution and brine, dried over magnesium sulfate and concentrated to afford the desired product, N-benzyloxy-2-hydroxy-2[1-(4-methoxybenzenesulfonyl)-cyclobutyl]acetamide, as an oil (0.72 grams, 100%).

(H) 2,N-Dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide

A solution of N-benzyloxy-2-hydroxy-2[1-(4-methoxybenzenesulfonyl)-cyclobutyl]acetamide (0.13 grams, 0.32 mmole) in methanol (30 mL) was treated with 5% palladium on barium sulfate (0.07 grams) and hydrogenated at 3 atmospheres pressure for 4 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 μm nylon filter and the filtrate was concentrated. The desired product, 2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide (0.061 grams, 65%), was isolated as a foam by flash chromatography on silica gel eluting successively with chloroform, 1% methanol in chloroform and 2% methanol in chloroform. MS m/z 314 (M-1).

Example 4

2,N-DIHYDROXY-2-[1-(4-METHOXYBENZENESULFONYL)CYCLOPENTYL]ACETAMIDE

2,N-Dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclopentyl]acetamide was prepared by a method analogous to that described in Example 3 using 4-methoxybenzenethiol and cyclopentyl bromide as starting materials. MS m/z 328 (M-1).

Example 5

2-{1-[4-(4-FLUOROPHENOXY)BENZENESULFONYL]CYCLOBUTYL}-2,N-DIHYDROXYACETAMIDE

2-{1-[4-(4-Fluorophenoxy)benzenesulfonyl]cyclobutyl}-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using 4-(4-fluorophenoxy)benzenethiol and cyclobutyl bromide as starting materials. MS m/z 394 (M-1).

4-(4-Fluorophenoxy)benzenethiol was obtained as follows. Chlorosulfonic acid (26 mL, 0.392 mole) was added dropwise to ice-cooled 4-fluorophenoxybenzene (36.9 grams, 0.196 mole) with mechanical stirring. When addition was complete, the mixture was stirred at room temperature for 4 hours. The mixture was then poured into ice water. The product, 4-(4-fluorophenoxy)benzenesulfonylchloride (18.6 grams, 33%) was collected by filtration and was dried in the air.

4-(4-Fluorophenoxy)benzene-sulfonylchloride (5.1 grams, 17.7 mmole) was added to an ice-cooled mixture of concentrated sulfuric acid (7 mL) and water (37 mL) with mechanical stirring. Zinc dust (6.2 grams, 95 mmole) was then added in portions. The cooling bath was removed and the mixture was allowed to stir at room temperature for 2 hours and at reflux for 3 hours. After cooling to room temperature, the mixture was quenched by addition of ice. The resulting mixture was extracted with toluene. The organic layer was washed with water and

saturated brine, dried over magnesium sulfate and evaporated to afford 4-(4-fluorophenoxy)benzenethiol as a white solid (3.3 grams, 84%).

Example 6

2-{1-[4-(4-FLUOROPHENOXY)BENZENESULFONYL]CYCLOPENTYL}-2,N-DIHYDROXYACETAMIDE

2-{1-[4-(4-Fluorophenoxy)benzenesulfonyl]cyclopentyl}-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using (4-fluorophenoxy)benzenethiol and cyclopentyl bromide as starting materials. MS m/z 408 (M-1).

Example 7

2-[1-(4-CYCLOBUTOXYBENZENESULFONYL)CYCLOBUTYL]-2,N-DIHYDROXYACETAMIDE

2-[1-(4-Cyclobutoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using 1-cyclobutoxy-4-cyclobutylsulfanylbenzene as starting material in step B. MS: 354 (M-1).

Example 8

2-[1-(4-BUTOXYBENZENESULFONYL)CYCLOBUTYL]-2,N-DIHYDROXYACETAMIDE

2-[1-(4-Butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using 1-butoxy-4-cyclobutylsulfanylbenzene as starting material as starting material in step B. MS: 356 (M-1).

Preparation A

4-(4-FLUOROPHENOXY)BENZENESULFONYLCHLORIDE

Chlorosulfonic acid (26 mL, 0.392 mole) was added dropwise to ice-cooled 4-fluorophenoxybenzene (36.9 grams, 0.196 mole) with mechanical stirring. When addition was complete, the mixture was stirred at room temperature for 4 hours. The mixture was then poured into ice water. The titled compound (18.6 grams, 33%) was collected by filtration and was dried in the air.

Preparation B

4-(4-FLUOROPHENOXY)BENZENETHIOL

4-(4-Fluorophenoxy)benzene-sulfonylchloride (5.1 grams, 17.7 mmole) was added to an ice-cooled mixture of concentrated sulfuric acid (7 mL) and water (37 mL) with mechanical stirring. Zinc dust (6.2 grams, 95 mmole) was then added in portions. The cooling bath was removed and the mixture was allowed to stir at room temperature for 2 hours and at reflux for 3 hours. After cooling to room temperature, the mixture was quenched by addition of ice. The resulting mixture was extracted with toluene. The organic layer was washed with water and

saturated brine, dried over magnesium sulfate and evaporated to afford the titled compound as a white solid (3.3 grams, 84%).

Preparation C

4-CYCLOBUTYLSULFANYLPHENOL

4-Hydroxybenzenethiol (10.0 grams, 79.3 mmole) was added to a suspension of sodium hydride (1.9 grams, 79.2 mmole) in N,N-dimethylformamide (50 mL). When evolution of hydrogen was complete and the mixture had cooled to room temperature, cyclobutylbromide (11.4 grams, 84.4 mmole) was added. The reaction mixture was stirred at room temperature for 2.5 hours and was then quenched by addition of water and 6 N aqueous hydrochloric acid solution. The mixture was extracted with diethyl ether. The organic extract was washed with brine, dried over magnesium sulfate and concentrated to afford a yellow oil. Roughly half of this material was chromatographed on silica gel eluting with 9:1:1 hexane/ethyl acetate/methylene chloride to afford the titled compound as a clear oil (8.85 grams).

Preparation D

1-CYCLOBUTOXY-4-CYCLOBUTYLSULFANYLBENZENE

A 60% suspension of sodium hydride in oil (1.97 grams, 49 mmole) was added to a solution of 4-cyclobutylsulfanylphenol(7.2 grams, 40 mmole) in N,N-dimethylformamide (25 mL). After hydrogen evolution was complete, cyclobutylbromide (6.4 grams, 47 mmole) was added. The reaction mixture was stirred at room temperature for 4 hours and then at 70°C in an oil bath for 16 hours. After cooling and quenching with water, the mixture was extracted with diethyl ether. The organic extract was washed with water and brine, dried over magnesium sulfate and concentrated to give an impure sample of the titled compound, an oil. This was used without without purification.

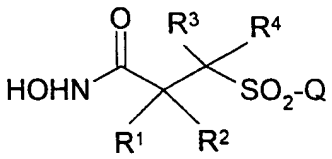
Preparation E

1-BUTOXY-4-CYCLOBUTYLSULFANYLBENZENE

A 60% suspension of sodium hydride in oil (2.2 grams, 55 mole) was added to an ice-cooled solution of 4-cyclobutylsulfanylphenol(8.85 grams, 49.1 mmole) in N,N-dimethylformamide (35 mL). After hydrogen evolution was complete, 1-bromobutane (6.7 mL, 58.9 mmole) was added. The reaction mixture was then stirred at room temperature for 16 hours. After cooling and quenching with water, the mixture was extracted with diethyl ether. The organic extract was washed with water and brine, dried over magnesium sulfate and concentrated to give an impure sample of the titled compound, an oil (11.2 grams). This was used without without purification.

CLAIMS

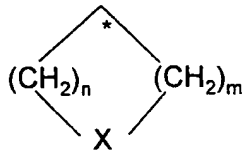
1. A compound of the formula



wherein R^1 is hydrogen, hydroxy, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl(C=O)O-, (C_1-C_6)alkoxy(C=O)O-, (C_6-C_{10})aryl(C=O)O-, (C_6-C_{10})aryloxy(C=O)O-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-; wherein said aryl moiety of said (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_6-C_{10})aryl(C=O)O-, (C_6-C_{10})aryloxy(C=O)O-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O- groups is optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

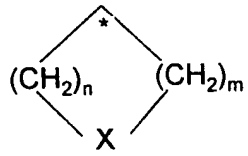
R^2 is hydrogen or (C_1-C_6)alkyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl(difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C=O)O-(C_1-C_6)alkyl , (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, $[(C_1-C_6)\text{alkyl}]_2$amino$(C_1-C_6)$alkyl, (C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, $R^5CO(C_1-C_6)$alkyl or $R^8(C_1-C_6)$alkyl; or R^3 and R^4 may be taken together with the carbon atom to which they are attached to form a (C_3-C_6)cycloalkyl or benzo-fused(C_3-C_6)cycloalkyl ring or a group of the formula



wherein the carbon atom bearing the asterisk is the carbon to which R^3 and R^4 are atttached, "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)alkyl(C=O)-, (C_1-C_6)alkoxy(C=O)-, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryloxy(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-; wherein each of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl or (C_3-C_6)cycloalkyl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-, (C_3-C_6)cycloalkyl, or benzo-fused(C_3-C_6)cycloalkyl ring may be optionally substituted on any ring atom capable of forming an additional bond by a substituent independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or when R^3 and R^4 are taken together with the carbon atom to which they are attached to form a group of the formula



then any of the carbon atoms of said ring, capable of forming an additional bond, may be optionally substituted by a substituent independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^5 is R^6O or R^6R^7N wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl; wherein each of said (C_6-C_{10})aryl and (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl groups may be optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or R^6 and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocycle selected from piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^8 is piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl,

piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, and (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

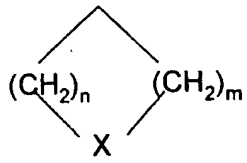
Q is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl wherein each (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl. perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

with the proviso that if either R^3 or R^4 is hydrogen, or if both R^3 and R^4 are hydrogen, then R^1 and R^2 can not both be hydrogen or R^1 must be hydroxy, (C_1-C_6)alkoxy, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C=O)O- (C_6-C_{10})arylalkyl(C=O)O-(C_1-C_6)alkyl or (C_6-C_{10})arylalkoxy(C=O)O-(C_1-C_6)alkyl;

and the pharmaceutically acceptable salts thereof.

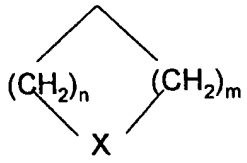
2. A compound according to claim 1, wherein R^1 is OH and R^2 is hydrogen.

3. A compound according to claim 1, wherein both R^3 and R^4 are (C_1-C_6)alkyl or R^3 and R^4 are taken together with the carbon atom to which they are attached to form an optionally substituted (C_3-C_6)cycloalkyl ring or benzo-fused(C_3-C_6)cycloalkyl ring or a group of the formula



wherein "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroalkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)alkyl(C=O)-, (C_1-C_6)alkoxy(C=O)-, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-; wherein each of said (C_6-C_{10})aryl and (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroalkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, and (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy.

4. A compound according to claim 2, wherein both R^3 and R^4 are (C_1-C_6)alkyl or R^3 and R^4 are taken together with the carbon atom to which they are attached to form a (C_3-C_6)cycloalkyl ring or benzo-fused(C_3-C_6)cycloalkyl ring or a group of the formula



wherein "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroalkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)alkyl(C=O)-, (C_1-C_6)alkoxy(C=O)-, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-; wherein each of said (C_6-C_{10})aryl and (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroalkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, and (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents independently selected from the group

consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy.

5. A compound according to claim 1, wherein R^3 and R^4 are taken together to form an optionally substituted (C_3-C_6)cycloalkyl ring.

6. A compound according to claim 2, wherein R^3 and R^4 are taken together to form an optionally substituted (C_3-C_6)cycloalkyl ring.

7. A compound according to claim 1, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

8. A compound according to claim 2, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

9. A compound according to claim 3, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

10. A compound according to claim 4, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

11. A compound according to claim 5, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

12. A compound according to claim 1, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

13. A compound according to claim 2, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

14. A compound according to claim 3, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

15. A compound according to claim 4, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

16. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

17. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

18. A compound according to claim 1, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

19. A compound according to claim 2, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

20. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

21. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

22. A compound according to claim 1, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

23. A compound according to claim 2, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

24. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

25. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

26. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(2*S*)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide,

3-[4-(4-fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide,

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide;

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclopentyl]acetamide,

2-[1-(4-cyclobutoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}-2,N-dihydroxyacetamide, and

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}-2,N-dihydroxyacetamide.

27. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, muscular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

28. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

29. A method for treating a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a

human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Inte ɪnaf Application No
PCT/IB 98/00101

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C317/44 C07C317/46 A61K31/16

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 20047 A (BRITISH BIOTECHNOLOGY) 14 October 1993 see claims 1,20 ---	1-3,26, 27
A	WO 95 09841 A (BRITISH BIOTECH) 13 April 1995 see claims 1,20 --- -/--	1-3,26, 27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of theinternational search	Date of mailing of the international search report
22 April 1998	08.05.98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 98/00101

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 9207 Derwent Publications Ltd., London, GB; AN 92-051997 XP002063103 "Amide cpds. which inhibit collagenase - useful for treating bone resorption diseases, epidermolysis bullosa, etc." & JP 03 294 252 A (YAMANOUCHI) , 25 December 1991 see abstract	1-3,26, 27
P,X	WO 97 24117 A (RHONE-POULENC) 10 July 1997 compound with CN(RN):193547-69-2 see claims 1,22,61,62	1-3,27
P,A	EP 0 780 386 A (F. HOFFMANN- LA ROCHE) 25 June 1997 see claims 1,28,30	1-3,26, 27

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/IB 98/00101

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 28-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/IB 98/00101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320047 A	14-10-93	AT 150452 T	15-04-97
		AU 3899193 A	08-11-93
		DE 69309047 D	24-04-97
		EP 0634998 A	25-01-95
		JP 7505387 T	15-06-95
		US 5525629 A	11-06-96
		ZA 9302501 A	08-11-93
WO 9509841 A	13-04-95	AU 7787594 A	01-05-95
		EP 0722438 A	24-07-96
		JP 9503222 T	31-03-97
		ZA 9407799 A	10-07-95
WO 9724117 A	10-07-97	AU 1529897 A	28-07-97
EP 780386 A	25-06-97	AU 7548296 A	31-07-97
		CA 2193178 A	21-06-97
		JP 9249638 A	22-09-97
		NO 965413 A	23-06-97
		PL 317604 A	23-06-97